REMARKS

Applicants have carefully reviewed and considered the Office Action mailed on February 26, 2008, and the references cited therewith, as well as the Advisory Action mailed August 13, 2008. Reconsideration and withdrawal of the rejections of the pending claims is respectfully requested.

The amendment of claim 6 to recite that the administration of glutamine plus carbohydrate increases the susceptibility of breast cancer cells to radiation therapy while protecting normal breast tissue from the effects of radiation is supported by the specification at page 5, lines 13-21 and by Example 9, e.g., at page 33, lines 5-11. This Example has recently been published as Y. Kaufmann et al., Nutr. Cancer, 60, 518 (2008) (copy enclosed).

Claims 6, 10-14, 44-53, and 55-56 are pending in this application.

I. The Rejection of the Claims under 35 U.S.C. §103

Claims 6, 10-14, 44-53 and 55-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Willmore et al. (U.S. Patent No. 5,248,697) in view of Shinal et al. (WO 00/69470) in view of Good et al. (U.S. Patent No. 6,666,811). This rejection is respectfully traversed.

Radiation therapy has been an effective treatment for breast cancer for many years. Radiation therapy kills cancer cells and healthy cells, including skin cells, in the treatment area. The skin in the area damaged by radiation may become reddened, dry, itchy, sunburned, or blistered and peeling (a condition called "moist desquamation"). Skin breakdown may occur, which may lead to an infection. Radiation injury to the skin causes significant pain and discomfort to the patient, impacts patient quality of life, and, in some cases, requires curtailing treatment. See specification, page 51, line 8 through page 52, line 10; see, www.radiologyinfo.org, "Breast Cancer" (included with Amendment filed June 24, 2008); see, www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them" (included with the Amendment filed June 24, 2008).

Applicants have made the paradoxical discovery that normal breast tissue can be protected against damage from radiation therapy by orally administering an aqueous composition comprising glutamine and carbohydrate to a patient afflicted with breast cancer and treated with

radiation therapy. At the same time that Applicants' method protects the breast tissue or associated upper body tissue against damage from the radiation therapy it sensitizes the cancer cells to killing by radiation therapy, thus effectively increasing the therapeutic index of the radiation therapy.

Applicants respectfully assert that the Examiner has not met the requirements for establishing a *prima facie* case of obviousness for the rejection of presently pending claims 6, 10-14, 44-53 and 55-56. The factual inquiries for the determination of obviousness, as set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), are as follows: 1) determine the scope and contents of the prior art; 2) ascertain the differences between the prior art and the claims at issue; and 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate the evidence of secondary considerations. Id. See also M.P.E.P. §2141; KSR International, Co. v. Teleflex Inc. et al., 127 S. Ct. 1727; 167 L. Ed. 2d 705; 82 U.S.P.Q.2D 1385 (2007). For the reasons presented hereinbelow, Applicants assert that the Examiner has not established a *prima facie* case of obviousness.

In fact, the last Amendment also contained a lengthy paragraph setting forth secondary considerations of non-obviousness that must be considered when resolving the obviousness question. This evidence, which goes to long-felt need, was not even mentioned by the Examiner in his conclusion that the claims were *prima facie* obvious in view of the art. It is not sufficient for the Examiner simply to note that radiation therapy applied to breast cancer patients causes side effects, as if the treatment or prevention of painful and potentially dangerous side effects related to the harm done to normal tissue would not represent satisfaction of a long-felt need in the art. The efficacy of the claimed method when administered to breast cancer patients undergoing radiation therapy is documented clinically in a patent obtained by one of the co-inventors, Suva et al. (U.S. Patent No. 7,186,517) (see Example 2).

A. Wilmore (U.S. Patent No. 5,248,697)

The Wilmore '697 patent discloses methods for maintaining or enhancing tissue or plasma levels of glutathione in a mammal by administering supranormal amounts of glutamine (or glutamine equivalents). Large amounts of glutamine are given generally disclosed to be

given parenterally to prevent the reduction in tissue glutathione levels associated with oxidative injury to the tissue of a mammal. See Cols. 5-6; claim 21.

The Examiner concedes that Wilmore does not teach the co-administration of carbohydrate and glutamine in radiation therapy, and that Wilmore does not teach the utilization of higher dosages of radiation because of the protective effects of the methods claimed by Applicants. See Office Action, page 3, second para.

In fact, Wilmore discloses radiation therapy for the treatment of cancer in only general terms. See Wilmore, col. 2, lines 46-57; col. 5, line 58 through col. 6, line 2. Although the Examiner relies on Wilmore at col. 7, line 66 through col. 8, line 9 as teaching the use of radiation therapy in breast cancer patients, Applicants note that that section actually describes a chemotherapy agent, 5FU, as a treatment for several carcinomas, including breast cancer. Thus, Wilmore does not teach the administration of glutamine to protect against breast or upper body tissue damage from radiation therapy administered to breast cancer patients while simultaneously sensitizing the cancer cells to radiation-caused death.

The failure of a reference to provide an explicit "negative teaching" is not the test of obviousness. However, the Examiner is requested to note that the disclosure in Wilmore that glutamine can reduce radiation-induced oxidative damage to radiation-damaged tissue represents a highly general and misleading report of the clinical results that were actually observed. Smith and Wilmore published their results in 1992 as F.R. Ziegler et al., "Clinical and Metabolic Efficacy of Glutamine-Supplemented Parenteral Nutrition after Bone Marrow Transplantation," Annal. Int. Med., 116, 821 (1992) (copy enclosed). The authors reported the results for 24 glutamine-supplemented patients and 21 control patients. Both groups were treated while recovering from BMT (40/45 patients received total body radiation). While the glutamine-supplemented patients had some improved clinical parameters, there was no difference in their "Cumulative Mucositis Scores" (see Table 4). Thus, susceptible normal tissue was not protected by glutamine, following radiation.

The Examiner is urged to consider that these are not contradictory reports by two different workers. Rather, the Annal. Int. Med. paper amounts to an expansion, explanation and an effective correction of the general disclosure in the Wilmore patent. Furthermore, these results were confirmed by P.R. Schloerb et al., J. Parent. Ent. Nutr., 17, 407 (1993) (copy

enclosed) who found no significant difference in oral mucositis between a group of 13 BMT patients receiving standard TPN and 16 patients receiving glutamine-supplemented TPN (Table IV, page 410, Col. 1, lines 4-6).

Similar results were reported by H.C.T. van Zaanen et al., Cancer, 74, 2879 (1994) (copy enclosed), who found that the glutamine analog, "glutamine dipeptide" had no effect on mucositis in patients undergoing chemotherapy. See Table IV.

The Examiner is requested to note that a reference which would lead one of ordinary skill in the art away from the claimed invention cannot render it unpatentably obvious. Dow Chem. Co. v. American Cyanamid Company, 2 USPQ 2d (1350)); In re Dow Chemical Co., 5 USPQ 2d 1529 (Fed. Cir. 1988); In re Grasseli et al., 218 USPQ 269 (Fed. Cir. 1983).

These clinical reports also support Applicants' arguments that the method of Wilmore is not intended to be practiced by oral administration of glutamine, whatever its utility. To begin, the terms "enteral" and "parenteral," as defined in Wilmore, do not include the term "oral" or anything arguably considered "oral." See Wilmore at col. 5, lines 53-57. Although Wilmore mentions that glutamine can be incorporated into the diet of a patient, the phrase "incorporation into the diet," without any additional definition, does not equate to "oral administration," but rather to incorporation into a "liquid diet" administered by enteral or parenteral feeding. Moreover, in each of Wilmore's three examples, the glutamine is given parenterally.

While the Examiner cites Col. 6, lines 22-48 as disclosing the "oral" administration of glutamine, the only disclosure in Wilmore relating to the "oral" administration of glutamine is directed to the use of glutamine following poisoning, not to its use during or following radiation treatment for cancer of any type. See Col. 6, line 35. The word "oral" is used only once (see col. 6, lines 45-48): "The route of administration will depend upon the severity of the poisoning, and an initial intravenous administration can be followed by subsequent oral doses, either alone or with food." Thus, at most, this paragraph discloses a combination of intravenous administration and oral dosing, to treat a subject that has been acutely poisoned.

The very next sentence states "[t]he administration of glutamine can be by enteral or parenteral means," and is followed by specifics and details on enteric and parenteral administration. See Wilmore, col. 6, lines 49-61. Wilmore continues, stating that "[g]lutamine can be administered either alone or as a dietary supplement. When used as a dietary supplement,

the glutamine can be mixed with an existing enteral or parenteral diet prior to administration to the patient." See col. 6, lines 62-65. Thus, when the entire disclosure of Wilmore is considered, it is evident that the methods in Wilmore are not intended to be carried out by the oral administration of glutamine.

B. Shinal et al.

Shinal et al. disclose compositions and methods for increasing cellular uptake of bioactive agents into mammalian cells upon topical or local contact of the cells with glutamine and carbohydrate. The compositions comprise an aqueous vehicle, a bioactive agent and carbohydrate. See Shinal et al. p. 3, lines 4-19. The bioactive agents are molecules that exert a therapeutic or nutritive effect on a mammal after absorption of an effective amount of the molecule by the target cells. Id., at page 5, lines 27-29.

However, the only use disclosed in Shinal et al. for their glutamine and carbohydrate compositions is to prevent or treat oral, nasal and esophageal lesions. See Shinal et al., p. 11, lines 25-29. There is no disclosure in Shinal et al. of orally administering an aqueous composition comprising glutamine and carbohydrate to protect a tissue remote from the administration site, such as breast or upper body tissue. In fact, neither Wilmore nor Shinal et al. disclose any effect of glutamine on breast tissue or upper body tissue. Shinal et al. also do not disclose the use of their methods and compositions to protect breast or upper body tissue from radiation damage, while sensitizing the cancer cells, so that the therapy achieves a higher therapeutic index, e.g., patient can be treated with higher doses of radiation before dose-limiting side effects occur.

C. Good et al.

Good et al. disclose methods of directed radiation therapy using radioactive implants to effectively control tumors without harming or injuring immediately adjacent tissues. See Good et al., col. 62, lines 44-45; col. 107, lines 62-65. Thus, Good et al. teach away from the administration of an exogenous chemical agent that protects normal tissues from radiation damage, while not similarly protecting cancerous tissue. One of ordinary skill in the art would not be motivated by Good et al. to use glutamine and carbohydrate as adjuvants to radiotherapy.

Instead, one of skill in the art would be led to use the radioimplants of Good et al. to treat cancer so that tumors can be controlled more effectively than by conventional radiotherapy, without harm to adjacent tissues. If anything, Good et al. provides evidence of a long-felt need in the art for methods to limit the damage to normal tissue caused by radiation therapy.

D. The combination of references

As stated by the Supreme Court in KSR v. Teleflex, "[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." KSR International, Co. v. Teleflex Inc. et al., 127 S. Ct. 1727; 167 L. Ed. 2d 705; 82 U.S.P.Q.2D 1385 (2007). An invention is not rendered obvious because Applicant did it and it worked. In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious"). Applicants assert that it is not obvious for a person of ordinary skill in the art to combine selected elements of the cited art, so as to yield the method set forth in the presently pending claims.

There is no logical reason that one of ordinary skill in the art would combine the teachings of Wilmore with Shinal et al. and Good et al. to solve the problem that Applicants have solved. It is respectfully submitted that one in possession of Wilmore and Shinal et al. might be motivated to parenterally or orally administer a mixture of glutamine and carbohydrate to a cancer patient to protect the patient's gastrointestinal tract tissue against the effects of cancer treatment. However, the efficacy of the parenteral administration of glutamine to "reduce or prevent starvation- or radiation-associated oxidative damage to tissues" as disclosed generally in Wilmore is contradicted by Wilmore's own publication. Taken as a whole, the publications discussed above would not lead the art worker to administer glutamine and carbohydrate orally or via TPN to achieve this effect in the tissue of the breast or associated external tissue of a breast cancer patient treated with radiation. The references simply do not disclose or suggest that the oral ingestion of glutamine plus carbohydrate would have any effect any specific body tissue other than oral, nasal or esophageal tissue, which tissue is topically contacted by the glutamine/carbohydrate composition. Of course, Applicants do not dispute that breast cancer is often treated with radiation therapy. But Good et al. would not motivate one of ordinary skill in

the art to treat any type of cancer with higher than normal doses of radiation in combination with anything other than the implants taught by Good et al.

The references, taken together or considered separately, do not suggest that orally administered glutamine and carbohydrate would have any impact on breast or upper body tissue, let alone provide the beneficial effect of reducing the well-known side effects of radiation therapy on normal skin while sensitizing cancer cells to killing by the radiation. For these reasons, a combination of Wilmore with Shinal et al. and Good et al. would not lead the art worker to Applicants' invention.

In view of the fact that the cited art does not even mention treatment/pre-treatment of breast cancer patients undergoing radiation, the Examiner is urged to consider that the presently-claimed method would not even be "obvious-to-try" in view of the large number of different types of cancer and tissues internal and external, that are affected by radiation therapy. Even if the prior art would render it obvious to try to reduce radiation damage to breast and associated upper body tissue, the Examiner is urged that there would be no reasonable expectation of success. "[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006). It requires more than routine experimentation to evaluate any glutamine/carbohydrate formulation on a particular class of cancer patients undergoing arduous therapy, particularly when the prior art teaches merely to pursue a "general approach that [seems] to be a promising field of experimentation" or "[gives] only general guidance as to the particular form of the claimed invention or how to achieve it [as does Wilmore]." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1993). This is particularly true in the present case, when Wilmore et al. failed to protect normal tissue in cancer patients undergoing BMT, using glutamine as a part of TPN.

Moreover, the Graham obviousness standards require an evaluation of the evidence of secondary considerations. See Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966); Ruiz v. AB Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000) ("Our precedents clearly hold that secondary considerations when present, must be considered in determining obviousness").

Evidence that an invention satisfied a long-felt need is pertinent to the question of obviousness. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540. 220 U.S.P.Q 303 (Fed. Cir. 1983).

In the present matter, the painful side effects of radiation therapy to the skin of breast cancer patients are well-known. See, www.radiologyinfo.org, "Breast Cancer" (included with previous amendment); see, www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them" (included with the previous amendment). Prior to Applicants' invention, breast cancer patients undergoing radiation therapy had no effective options for treating radiation-damaged skin. Patients were advised to "be gentle" on their skin, or not to wear tight clothes or to use soft fabrics in order to not further irritate the damaged skin. See www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them," at page 13. In addition, there were no medically recommended options for preventing breast tissue damage prior to radiation therapy. Applicants' composition protects the breast tissue or associated upper body tissue against damage from the radiation therapy, while sensitizing cancer cells to killing, so that the subject can be treated with a higher dose of radiation without DLT. Applicants' discovery that breast tissue can be protected against damage from radiation therapy by orally administering an aqueous composition of glutamine and carbohydrate to a patient afflicted with breast cancer and treated with radiation therapy fulfills an important, long-felt need for patients undergoing treatment for breast cancer.

These references, either alone or taken in combination, do not render the presently claimed invention obvious. Therefore, withdrawal of this rejection is appropriate and Applicants respectfully request that the rejection under 35 U.S.C. ' 103(a) be withdrawn.

II. The Double Patenting Rejection

Claims, 6, 10-14, 44-52 and 55-56 were rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 7,186,517, in view of Shinal et al. (WO 00/69470) and Good et al. (U.S. Patent No. 6,666,811). This rejection is respectfully traversed.

As set forth in the section of the M.P.E.P. on obviousness-type double patenting, the present situation is one in which the claims of an application are subject to rejection over the claims of an issued patent having a later effective filing date. M.P.E.P. § 804(II)(B)(1)(b) (8th

ed., rev. 5, 2006). Thus, the claims in question are subject to a two-way test for obviousness. In the present case, the requirements for a two-way obviousness test are fully met. Applicants could not have filed the claims in the same application because the monitoring test claimed in the '517 patent was invented after the tissue protection method claimed in the present application. Also, the ownership of the '517 patent and the present application are not the same. The requirement for "administrative delay" is moot here, because the '517 patent was examined in a different Group Art Unit. Furthermore, there is no evidence that Applicants have not prosecuted this application diligently, or have attempted to delay its issuance. If the two-way test is applied, it is clear that the monitoring method is patentably distinct from the method of the present claims, as it requires determining the presence of a marker protein that is not disclosed or suggested in the present claims or specification. Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. Alternatively, withdrawal of the obviousness-type double patenting rejection will reduce the issues to be decided on Appeal. The Examiner is invited to telephone Applicants' attorney at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 26th day of November, 2008.

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